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DATE MAILED: 01/26/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire Three (3) month(s), _____ ~~days~~ from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 39-61 are pending in the application.
   Of the above, claims 48 and 49 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 39-47 and 50-61 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

The restriction requirement made in Paper #4, and made FINAL in Paper #7, in the parent application S.N. 07/852390 is reiterated. Applicants' election with traverse of Group I in Paper No. 6 is reaffirmed and prosecution is being continued on the elected invention.

Claims 48 and 49 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 6.

This application contains claims 48 and 49 drawn to an invention non-elected with traverse in Paper No. 6. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 C.F.R. § 1.144) M.P.E.P. § 821.01.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 39-47, 50, 51, 55 and 61 are rejected under 35 U.S.C.

§ 103 as being unpatentable over Sanders et al. in view of

Alberts et al. or Watson et al.

This rejection is maintained for reasons of record in the previous Office Action (Paper #10) and for reasons outlined below.

Applicants recite a recombinant, amplifiable, DNA sequence encoding the amino acid sequence of a hamster glutamine synthetase (GS) enzyme, a recombinant expression vector containing said GS sequence and a host cell transformed with said sequence.

Sanders et al. (AR, EMBO, Vol. 3, 1984, pp. 65-71, See whole document, particularly p. 69) recite the cloning of at least part of the hamster GS gene and the amplification of said gene in methionine sulphoximine resistant cells. Sanders et al. do not recite generation of an expression vector capable of expressing the GS gene or host cells transformed with said gene.

Alberts et al. ("Molecular Biology of the Cell", 1983, pp. 184-193) and Watson et al. ("Recombinant DNA, A Short Course", 1983, pp. 184-193) recite the generally routine steps of cloning a gene and expressing a cloned gene of interest in transformed host cells.

Applicants invention is essentially a logical conclusion to the work of Sanders et al. Applicants indeed recite that the methods used by Sanders et al. were duplicated in the instant disclosure (See Specification, Page 17, 2nd paragraph); therefore, given the teachings on preliminary identification of a

portion of the GS gene (Sanders et al.) it must be considered that the subsequent cloning, sequencing and expression of the entire GS gene by following of the routine cloning and expression steps outlined by Alberts et al. and Watson et al. would have been obvious to an artisan of ordinary skill in the art. An ordinary skilled artisan, seeking to isolate, clone and express an amplifiable gene, such as the GS gene, for potential use in co-amplifying an additional foreign gene of interest, would have been motivated to use the teachings of Sanders et al. on a preliminary characterization and cloning of at least part of the GS gene combined with the routine steps of cloning, sequencing and expressing genes of interest in microorganisms recited by Alberts et al. and Watson et al. in order to isolate, clone and express the GS gene.

Applicants have traversed this rejection by asserting that "...the Examiner does not state why a skilled artisan should seek to clone, sequence and express a gene involved in any metabolically important pathway." (Page 2 of the amendment filed 12/14/94) and in particular, the GS gene. Applicants assert that there was little motivation to clone the GS gene and only applicants discovery of the use of said gene to amplify foreign genes in host cells (even in the presence of the endogenous GS gene) provided incentive to clone the GS gene. With regard to the teachings of the Sanders et al. reference on the cloning of the Chinese hamster GS gene, applicants indicate that said

reference provided no evidence that the GS gene was actually cloned and that the skilled artisan would have been skeptical of the teachings of Sanders et al. and would not have been motivated to complete the studies of Sanders et al.

Applicants arguments made in the amendment filed 12/14/94 have been carefully considered but are not deemed to be persuasive.

First, it is noted that Sanders et al. provided several motivations for cloning the GS gene, for example, Sanders et al. indicated that the GS gene product "...is responsible for the conversion of glutamate and ammonia to glutamine, which has been described as the most versatile of all amino acids...", that GS levels "...may be regulated in vivo and in vitro as a result of cellular differentiation, glucocorticoid hormone levels and medium glutamine levels..." and thereby be important in understanding cellular differentiation, etc. and finally that "Gene amplification has also been reported as an oncogenic phenomenon." (Page 65, right column).

Second, applicants assertion that there was no evidence that Sanders et al. cloned the GS gene is directly contradictory to applicants' sworn statements in the instant specification. Specifically, applicants indicated in the instant specification, the following: "Recently Sanders and Wilson (Sanders P.G. and Wilson R.H., The EMBO Journal, 3, 1, 65-71, 1984) have described the cloning of an 8.2 kb BglII fragment containing DNA coding for

GS from the genome of an Msx resistant Chinese hamster ovary (CHO) cell line KGIMS." Applicants also indicated that the procedures of Sanders et al. were used to isolate the GS gene from CHO-KG1 cells (See pages 15-17 of the instant specification). It is submitted therefore that applicants cannot have it both ways. Either the applicants' sworn statements in the specification are incorrect and potentially a best mode rejection may be warranted or applicants assertions in the Remarks section of the amendment filed 12/14/94 are incorrect.

Finally, with regard to applicants assertions that the claimed invention is unobvious because applicants have demonstrated the amplification of an exogenous GS gene in the presence of the endogenous GS gene, it is noted that this argument is not persuasive because the claims as currently presented, do not recite this limitation and, moreover; said arguments appear to pertain more to the method claims which were issued in U.S. Patent #5,122,464.

Claims 52-54 and 56-60 are rejected under 35 U.S.C. § 103 as being unpatentable over Sanders et al. in view of Alberts et al. or Watson et al. all further in view of Axel et al. (AA).

This rejection is maintained for reasons of record in the previous Office Action (Paper #10) and for reasons outlined below.

Applicants recite the use of a recombinant DNA vector

comprising the amplifiable marker GS gene sequence and further comprising a second DNA sequence encoding a non-GS protein of interest, with said genes linked so as to result in amplification of the non-GS coding sequence. Applicants further recite the specific plasmids comprising the GS and tPA genes (pSVLGS.tPA16 and pSVLGS.tPA17), and use of recombinant plasmids comprising the GS gene to confer survivability to cells lacking adequate GS activity.

Sanders et al., Alberts et al. and Watson et al. are applied as above. Sanders et al., Alberts et al. and Watson et al. do not teach co-amplification of two different linked or un-linked DNAs.

Axel et al. (AA, U.S. Patent # 4399216, 8/16/83, See whole document, particularly the abstract and Column 3, 1st paragraph of "Summary" section, Column 5, last 2 paragraphs and Claim 54) recite the co-amplification of two different linked or un-linked DNAs, one DNA being an amplifiable gene coding for a dominant selectable marker such as drug resistance and the second DNA being a gene coding for a protein of interest.

Applicants invention is essentially an obvious variation on the teachings disclosed by Axel et al. It is noted that Axel et al. recite the linking, in a plasmid vector, of a dominant amplifiable, selectable, gene with a cloned gene of interest and the selection conditions for identification of cells which have acquired, amplified and expressed the selectable phenotype and

hence the second cloned gene of interest. Therefore, an ordinary skilled artisan, seeking to amplify and express a gene of interest (e.g. tPA) by linking said gene to a dominant, amplifiable, selectable gene would have been motivated to use the teachings of Sanders et al. on the partial identification and cloning of the amplifiable dominant selectable GS gene combined with the teachings of Alberts et al. and Watson et al. on the routine steps involved in cloning, sequencing and expressing a gene of interest further combined with the teachings of Axel et al. on a method of amplifying and expressing a gene of interest by linking said gene to a dominant selectable gene (the GS gene would fall into this category) and selecting for cells containing the two amplified genes under conditions suitable for survival of the cells containing the amplified dominant selectable gene in order to generate a recombinant vector with the dominant selectable amplifiable gene (GS) linked to a second gene of interest, transform suitable host cells (i.e. CHO-K1 cells) and culture cells under conditions which would permit selection of cells carrying the amplified genes. It would have been obvious to an ordinary skilled artisan, endeavoring to develop a procedure for amplification and expression of a gene of interest to use the teachings of Sanders et al. on the partial characterization of an amplifiable dominant selectable gene (GS) combined with the teachings of Alberts et al. and Watson et al. on the routine steps necessary to successfully clone, sequence

and express a gene of interest further combined with the teachings of Axel et al. on the amplification and expression of genes of interest by linking said genes to amplifiable and selectable genes (e.g. GS) and selection of said gene combinations by culturing the transformed cells under selective conditions permitting survival of the cells which have acquired the gene combination in order to generate expression vectors (and transformed cells) comprising the GS gene and a gene encoding a protein of interest and culturing said transformed cells under conditions allowing for amplification and expression of said gene combinations.

Applicants have traversed this rejection by asserting that Axel et al. only taught co-amplification of the DHFR system wherein the exogenous DFHR genes are introduced into cells without an endogenous DHFR gene. Applicants also assert that "...the GS gene has been found to be a selectable and amplifiable marker even in cell lines which, because they possess an endogenous GS gene, survive perfectly well under conditions of glutamine starvation." (Page 6 of the instant amendment). Finally, applicants assert that the examiner presents no evidence that the GS gene would function in the method described by Axel et al. and that the instant invention provided a significant advance in the art compared to the method disclosed by Axel et al.

Applicants' arguments have been carefully considered but are

not deemed to be persuasive. First, it is again noted that applicants' arguments with regard to amplification of the GS gene and a foreign gene sequence in cells containing a normal endogenous GS gene do not appear to pertain to the instant claims. Second, with regard to applicants' assertions that "Previous co-amplification systems, such as the DHFR system require that the cell line used be deficient for the amplifiable gene." (Page 6 of the instant amendment), it is noted that Axel et al. recited the following with regard to cells which could be used in co-amplification systems:

"Cotransformation with dominant-acting markers should in principle permit the introduction of virtually any cloned genetic element into wild-type cultured eucaryotic cells. To this end, a dominant-acting methotrexate resistant, dihydrofolate reductase gene from CHO A29 cells was transferred to wild-type cultured mouse cells. By demonstrating the presence of CHO DHFR sequences in transformants, definitive evidence for gene transfer was provided. Exposure of these cells to elevated levels of methotrexate results in enhanced resistance to this drug, accompanied by amplification of the newly transferred gene. The mutant DHFR gene therefore, has been used as a eucaryotic vector, by ligating CHO A29 cell DNA to pBR322 sequences prior to transformation. Amplification of the DHFR of the DHFR sequences results in amplification of the pBR sequences. The use of this gene as a dominant-acting vector in eucaryotic cells will expand the repertoire of potentially transformable cells, no longer restricting these sort of studies to available mutants." (Column 8).

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by

the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention.

The plasmids pSLGS.tPA16 and pSVLGS.tPA17 are necessary for practicing of the instant invention in that these recombinant plasmids contain the DNA sequences coding for the GS gene, a foreign gene (tPA) and the sequences necessary for expression and/or amplification of said DNA. Given that the plasmids are essential for enablement of the invention and have not been described in sufficient detail to enable one of ordinary skill in the art to exactly duplicate said plasmids, a deposit of said plasmids is deemed necessary (See attachment on "Deposits of Biological Materials" supplied in Paper #7).

Claims 53 and 54 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 39, 40, 44-47, 50-52, 55, 56, 58, 60 and 61 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a hamster GS gene, vectors containing said gene and methods of endowing cells with the ability to survive in a medium lacking glutamine or co-amplifying a gene of interest wherein said methods comprised transforming cells with vectors containing the hamster GS gene. See M.P.E.P. §§ 706.03(n) and 706.03(z).

This rejection is maintained for reasons of record in the

previous Office Actions (Papers # 10 and 14) and for reasons outlined below.

Applicants recite claims to recombinant DNA sequences encoding (amplifiable) mammalian or rodent GS genes but have enabled only the hamster GS gene and have not recited how one of skill in the art would have gone about isolating and identifying GS genes from any or all possible mammalian or rodent species so as to incorporate said genes into vectors or endowing cells with the ability to survive in media lacking glutamine or co-amplify genes on interest. To identify GS genes from any mammal or rodent species it would have been necessary to derive cell lines from that species (if they can be derived), select for mutants defective in GS activity (if they can be generated), isolate the regions of heterogeneity in the mutant and normal cell lines, fine map the sequences of interest, determine if they encode a GS gene, determine if the GS gene could be amplified and finally determine if a foreign gene linked to the GS gene could have been co-amplified. Given these steps and the uncertainties inherent in each step, given that the sequence homologies between the hamster GS gene and any other mammalian or rodent GS gene were totally unknown, given that applicants have provided no teachings on what other GS genes could have been amplified or used to co-amplify foreign genes of interest, it is considered that undue experimentation would have been required to practice the instant invention.

Claims 57 and 59 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to CHO-KI myeloma cells. See M.P.E.P. §§ 706.03(n) and 706.03(z).

This rejection is maintained for reasons of record in the previous Office Actions (Papers #10 and 14) and for reasons outlined below.

It is unclear if myeloma cell lines can be generated from all mammalian species (Claim 57) or from any animal species (Claim 59). To practice the instant invention, an ordinary skilled artisan would need to generate myeloma cell lines from any animal or mammal species of interest. Given that myeloma cell lines have been isolated from only a few of the thousands of potential animal species in question, given the extensive diagnostic, clinical procedures and in vitro cell culture techniques involved in identification, characterization, cloning and maintaining a new myeloma cell line and given that myeloma cell lines may not be able to be generated from all mammalian or animal species and given that applicants have provided no teachings on the generation of myeloma cell lines from any animals of interest, it is considered that the skilled artisan would have had to have practiced undue and excessive experimentation to practice the instant invention.

Applicants have traversed the above 35 USC 112, 1st paragraph, Scope, rejections by asserting that the GS gene could

be amplified in any cells derived from any mammal and that cell lines were not required to practice the instant invention by techniques known in the art.

Applicants' arguments are not persuasive because applicants have not disclosed, in the instant specification, how one of skill in the art would have isolated the GS gene from any mammal of choice (i.e. what types of probes would have been useful, what specific hybridization conditions would have been used, etc.), how one of skill would have generated myeloma cell lines from any mammal of choice, how one of skill would have amplified the GS gene in cells of choice (i.e. how one of skill would have generated Msx-resistant cell lines from any mammal, how one of skill would have developed expression vectors capable of functioning in the cell lines of choice, etc.). Clearly, given the lack of guidance by applicants, given the broad scope of the instant claims and given the lack of prior art teachings on the nature of GS genes from any other mammals, it must be considered that enablement of the full scope of the instant claims would have required the skilled artisan to have practiced undue and excessive experimentation which would not have been, in any fashion, routine. It is also noted that with regard to the broad scope of the applicants claims, the unpredictability in the procedures required to reduce the instant invention to practice and the lack of guidance by applicants in these areas, that the Courts have held that the first paragraph of 35 USC 112 requires

that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art and that in cases involving unpredictable factors such as physiological activities, the scope of enablement varies inversely with the degree of unpredictability of the factors involved. (See In re Fisher 166 USPQ 18 CCPA 1970).

Claim 44 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 is indefinite in that it is unclear what "high stringency conditions" encompass and it is unclear what DNA sequence comprises "a part thereof from a different species". The phrase "high stringency conditions" has potentially many different meanings and since applicants have not defined said conditions in the instant specification, it is unclear what conditions are encompassed by this term. Also, the phrase "a part thereof" potentially reads on the entire GS gene sequence minus one nucleotide down to a single nucleotide of the GS gene. The metes and bounds of the instant claim language need to be more precisely defined.

Applicants have traversed this rejection by asserting that "high stringency" hybridization conditions were universally known

in the art and have provided copies of pages from Maniatis et al. to illustrate this. Applicants also ...

Applicants arguments have been considered but are not persuasive. The teachings of Maniatis et al. do not define "high stringency" conditions but only the parameters that need to be considered in designing hybridization conditions. Applicants' assertion that high stringency conditions pertain to the "results" of a combination of these parameters is unclear as the result of the hybridization is dependent on the conditions utilized in the hybridization process. Without a definition of the high stringency conditions, the results of hybridization will vary.

With regard to the metes and bounds of the claim language, it is still noted that the instant claims still read on undefined parts of the GS gene from some other species, i.e. the entire gene, a 20 nucleotide sequence, a 30 nucleotide sequence, etc. and is therefore unclear.

With regard to the reference provided with the instant amendment, said reference was considered only with respect to its supporting or not supporting applicants' arguments.

No claims are currently allowable in this application.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published

in the Official Gazette, 1156 OG 61 (Nov. 16, 1993) and 1157 OG 94 (Dec. 28, 1993) (See 37 CFR 1.6(d)). The CM1 Fax Center number is (703) 305-3014. NOTE: If applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication should be directed to Examiner David Guzo at telephone number (703) 308-1906. The examiner can normally be reached on Monday - Thursday from 8:00 AM - 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Richard A. Schwartz, can be reached at (703) 308-1133.

Inquiries of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist, whose telephone number is (703) 308-0196.

DAVID GUZO
PATENT EXAMINER
GROUP 1800

DAVID GUZO

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January 9, 1995